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"Design, Development and Evaluation of Novel Nanoemulgel for Topical Drug Delivery System"

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1. Abstract of proposed work plan/ problem:

Recently utilizing nanoemulgel as a vehicle for deliver the drug through topical drug delivery has been increased. The purpose of the present study was to develop a nanoemulgel formulation and characterize for topical drug delivery system. Homogenization method was adopted for various oil-in-water nanoemulsion preparations. The prepared nanoemulsions were characterized for its particle size, polydispersity index, zeta potential, SEM, TEM, pH, viscosity, drug content, spreadability and its *in-vitro* release studies. Drug excipient compatibility study results reveals that the excipient used in the nanoemulsion is having compatibility. Based on its *in-vitro* release studies of optimized formulation showed higher release compared to other formulations. Incorporating the preparation of nanoemulsion with gel base to produce nanoemulgel and characterized. The In-vivo studies and In-vitro drug release kinetics profile of the optimized formulation was compared with the nanoemulgel. In conclusion, the results of the present investigation suggested that the developed nanoemulgel formulation can be used as a vehicle for improve solubility and enhancement of bioavailability through topical drug delivery system.

Keywords: Nanoemulsion, Gel base, Nanoemulgel, In- vivo studies, In -vitro drug release kinetics.

2. Introduction:

Since the dawn in pharmaceutical culture in Mesopotamia (2600 B.C.) by the use of water, and plant for the treatment of ailment, pharmacists are able to develop the era of modern dosing systems. Researches in this field have introduced several routes of administration to deliver the developed modern dosage forms. The dosage forms are mostly dependent on the physicochemical characteristics of the active compound. Recent trend of synthesis drug development or during high throughput screening leads towards development of lipophilic active pharmaceutical agents. Recent statistical reports on poor aqueous solubility of new chemical entities (NCE) (70%) has crossed the initial report of around 40% NCE with poor solubility. Lipophilic characteristics of the newly developed drug molecules manifest the problems like poor oral bioavailability, erratic absorption, intra- and inter-subject pharmacokinetic variations and lack of dose proportionality. To overcome those issues to focus on solubility enhancement, formulation approach is a continuous developing process. Different strategies such as physical modification, chemical modification and formulation development can be used to improve the solubility of poorly soluble drugs. There have been numerous formulation approaches to improve the solubility of poorly aqueous soluble drugs such as particle size reduction to deliver through nanocarrier system, crystal engineering, amorphous formulation, several lipid formulations approaches, etc. Newer lipid formulation techniques, viz: incorporation of lipophilic component in inert lipid vehicle, formation of microemulsion or nanoemulsions, self-emulsifying formulations, liposomes, solid lipid nanoparticles or lipid nanocarriers are becoming increasingly popular to overcome these problems of lipophilic properties of compounds. Consequently, several route of administration have been explored to deliver those formulations based on its distinct advantages and disadvantages on target site, severity of disease, patients' age and condition, available dosage form and finally for the compliance of the users.

Oral route is the most preferred route anchored in patient compliance, however, oral administration is more prone to result in hepatic first pass metabolism, leading towards requirement of higher dose. Further, gastric irritation is the major limitations for the presence of surfactants in the lipid based formulations; simultaneously the distribution of drug throughout the body can lead to unavoidable side effects. Hence, to stay away from such unacceptable issues, the non-invasive, non-paining, non-irritating topical delivery of

formulation is an alternate way associated with several advantages such as delivery of drug to specific site of action with reduced systemic toxicity, avoidance of first pass metabolism and gastric irritation, increasing release rate of drug from formulation to improve percutaneous absorption and sometime topical application related to increase bioavailability with sustained release profile.

Besides its advantages described, traditional transdermal formulations, viz: ointments, creams, lotions are in accord with many disadvantages such as sticky nature, lack of spreadability, stability issue, etc., ultimately leading to patient incompliance. Modernization of transdermal delivery by the formulation revealed transparent gel and emulgel with greater patient compliance and improved efficacy. Thus, these formulations are gaining interest both in cosmetics industries, as well as in pharmaceutical industries. In spite of lots of advantages of gel and emulgel formulations, delivery of hydrophobic drug still remains a big hurdle to cross over. Moreover, skin penetration through stratum corneum is also a great concern to the researchers for the systemic activity of the transdermal delivery. Literatures suggest that nanosized topical formulations can enhance permeability of the active moiety by disrupting the lipid bilayer as evident from the distinct void and empty spaces in the nanoemulsion treated skin samples and extent retention of the drug at the site of action. Nanoemulsion bears much hope being isotropic, transparent (or translucent) heterogeneous mixture composed of two media (oil and aqueous), one phase is dispersed in another and stabilized by an interfacial film of surfactant molecules. Studies suggested that nanoemulsions have a higher drug solubilization capacity than simple micellar solutions, and their thermodynamic stability offers advantages over unstable dispersions, such as emulsions and suspensions, because they can be manufactured with little energy input (heat or mixing) and have a longer shelf-life. Regardless of lots of advantages of nanoemulsion, topical application is limited due to its low viscosity and spreadibility. Researchers have solved the problems associated with nanoemulsion for transdermal delivery through a simple conversion of nanoemulsion to nanoemulgel. Nanoemulgels are nanoemulsion, either of oil-in-water (*o/w*) or water-in-oil (*w/o*) type which further convert to nanoemulgel by using gelling agent. Nanoemulsion ensures adequate localization and dispersion of the drug by adequate percutaneous absorption within the skin to enhance its local efficacy and/or through the skin

to the circulation to polish its systemic effect and even can cross the rigid blood-brain-barrier to offer added advantages in CNS activity.

The outcomes in the field of pharmaceutical formulation development, study on nanoemulgel focuses on development of vast number of delivery system viz: transdermal, dental, vaginal, ocular, nose to brain nanoemulgel for treatment of various local as well as systemic ailments so that focusing on formulation overview and penetration aspects of emulgel, characterization of the nanoemulgel, current market products on nanoemulgels and its advantages and delivery of antifungal agents through nanoemulgel delivery. The screening for nanoemulgel formulation combined with its formulation overview and pharmacokinetic and pharmacodynamic parameters of the published research works on nanoemulgel with different pharmaceutical products. Therefore, the aim of the present study is to give an overview on the selection criteria of the basic component for nanoemulgel and its positive/negative role in experimental results on pharmacokinetics, pharmacodynamics and safety of the drug. Connecting section of the article will reveal the components and selection criteria for the achievement of targeted objective.

3. Review of Literature and Development in the subject (Previous work done in the relevant area):

1. Prashant Kesharwani et al. (2017)

The researcher studied that nanoemulgel emerging transdermal delivery tool has proved that show surprising upshots for the lipophilic drugs over other formulations. This lipophilic nature of majority of the newer drugs developed in this modern era resulting in poor oral bioavailability, errati absorption and pharmacokinetic variations. Therefore, this novel transdermal delivery system has been proved to be advantageous over other oral and/or topical drug delivery to avoid such disturbances. These nanoemulgels are basically oil-in-water nanoemulsions gelled with the use of some gelling agent in it. This gel phase in the formulation is non-greasy which favors user compliance and stabilize the formulation through reduction in surface as well as interfacial tension. Simultaneously, it can be targeted more specifically to the site of action and can avoid first pass metabolism and relieve the user from gastric/systemic incompatibilities. This brief review is focused on nanoemulgel as a better topical drug delivery system including its components screening, formulation method and recent pharmacokinetic and pharmacodynamic advancement in research studies carried out by the scientists all over the world. Therefore, at the end of this survey it could be inferred that nanoemulgel can be a better and effective drug delivery tool for the topical system.

2. Laxmana P S et al. (2017)

In this work, cyclobenzaprine nanoemulsion has been developed. The optimized nanoemulsion formulation, which exhibited maximum drug release, was formulated as novel nanoemulgel of cyclobenzaprine with suitable viscosity for topical administration. The *in-vitro* results revealed that the developed nanoemulsion based gel containing cyclobenzaprine hydrochloride has great potential to provide better therapeutic effect locally through topical application.

3. Syamala U et al.(2014),

In this study evaluated that the ex-vivo skin permeation of butenafine nanoemulgel formulation. The skin permeability of the drug was more (20%) compared to the marketed cream (18%). The retention amount of drug on the skin was also more (31%) in nanoemulgel preparation than the cream (20%).

4. Sampati S et al. (2015)

In this study, itraconazole nanoemulgel was developed by ultrasonication after dissolving the drug in eugenol by heating with lecithine and sodium cholate as surfactants. Optimized nanoemulsion was converted to nanoemulgel by using carbopol 934 and the pH was adjusted by triethylamine. Here, the researchers used 0.1% limonene in the formulation as permeation enhancer as well as odor masking agent. Nanoemulsion based hydrogel of itraconazole showed promising penetration and *in vitro* release when compared to the drug solution. Interestingly, the formulation showed sustained release profile which might be helpful in reduction of the dosing frequency

5. **Pund et al. (2015),**

In that study researcher evaluated the safety of their developed leflunomide nanoemulgel formulation by histopathological study in rat to find out whether use of nanoemulgel alters the skin integrity or produce any skin irritation or toxicity. No abnormal histopathological changes in the rat abdominal skin were observed after 12 h of nanoemulgel treatment. No haemorrhage, necrosis or ulceration was observed on the treated skin.

6. Radhika & Guruprasad (2016),

In that study researcher evaluated the anti inflammatory activity of flurbiprofen nanoemulgel by carrageenan induced rat paw edema method. The efficiency for rate paw edema inhibition after 12 h was found to be higher for nanoemulgel (85.2%) compared to the conventional gel (68.0%) formulation.

7. Omar Samia1 et al. (2012),

In this study demonstrated that CBZ-loaded mucoadhesive nanoemulgel for intranasal use could be a promising new brain targeting delivery system via the olfactory mucosa for the treatment of epilepsy at lower doses with consequent decrease in the peripheral side actions of CBZ.

8. Rambharose et al. (2017),

In this study, LLA1E, which is a recently reported novel transdermal permeation enhancer, was successfully used as an oily phase excipient in the formulation of TNEGs. The formulated TNEG, with a low drug loading of 0.25% w/w, displayed high incorporation efficiency and superior *ex vivo* transdermal permeation enhancement of TNF. This is the first study to report the formulation of a TNF NE and NEG system, as well as to successfully

deliver therapeutically relevant amounts of TNF via the transdermal route using a nano drug delivery system. The TEER and histological studies revealed that the effects of the TNEG on the skin were temporary. It can therefore be concluded that LLA1E is a promising oily phase excipient in the formulation development of lipid based transdermal nano formulations and that the proposed TNEG in this paper has the potential to revolutionize HIV/AIDS treatment.

9. Ramakrishna Sistla et al. (2016),

The investigation described above provided evidence for the use of emu oil as an oil phase in pharmaceutical formulations. To our knowledge, this is the first report in the direction of development of novel formulations employing emu oil to address the problems of poor permeation properties for bioactive compounds such as curcumin. From our findings, we conclude the possibility of using emu oil based curcumin nanogels for transdermal delivery of curcumin as a suitable approach to bypass its first pass metabolism and thus eliciting enhanced anti-oxidant, anti-inflammatory and analgesic activity in the joint synovium, which may ameliorate arthritis. However, further investigation is required to enhance the curcumin loading to match the human clinical dose of curcumin in treatment of human arthritis.

10. Nagib A. Elmarzugi et al. (2015),

The researcher studied that the Nanoemulsion is referred type of emulsion with uniform and extremely small droplet size in the range of 20-200 nm. Nanoemulsion provides numerous advantages over other carrier such as polymeric nanoparticle and liposomes, including low cost preparation procedure, high hydrophilic and lipophilic drug loading system to enhance the longer shelf live upon preserving the therapeutic agents. Incorporating the preparation of nanoemulsion with hydrogel matrix to produce nanoemulgel exhibited by the two separate systems that forming it. Nanoemulgel possesses the properties of thixotropic, non-greasy, effortlessly spreadable, easily be removed, emollient, not staining, soluble in water, longer shelf life, bio-friendly, translucent and agreeable appearance.

4. Objectives of Research/ Proposed Hypothesis:

Aim: Design, Development and Evaluation of Novel Nanoemulgel for Topical Drug Delivery System

Objectives:

- To improve the bioavailability of drugs
- To prolong the release over a predetermined time period.
- To reduce the amount of dose.
- To decreases the side effects and effectively management of topical drug delivery system
- Design, Develop and Evaluate of Novel Nanoemulgel for Topical Drug Delivery System

5. Methodology to be adopted:

1. Literature survey.

2. Selection and Collection of Drugs & excipients

a. Drug: Antifungal:

Luliconazole or Posaconazole etc.

b. Selection of Excipients: Viscosity modifiers, Gelling agent, Solvents, Preservatives etc.

3. Experimental Work:

a. Preformulation studies:

- Procurement of drug sample(s)
- Organoleptic properties
- Solubility analysis
- Melting point
- Partition coefficient
- UV spectral analysis
- FT-IR spectral analysis
- Differential scanning calorimetry (DSC)
- X-Ray Diffraction (XRD) analysis

b. Drug excipients compatibility study

c. Preparation and Evaluation of Nanoemulgel: 3 major steps Nanoemulgel preparation

Step I: Preparation and Evaluation of Nanoemulsion:

- Preparation of nanoemulsion by these three methods like Ultrasonicators, high pressure homogenisers, microfluidizers,

Evaluation of Nanoemulsion:

- Physical Examination
- Transmission electron microscopy (TEM)
- Scanning Electron Microscope (SEM)
- Droplet size, polydispersity and zeta potential
- Viscosity determination
- pH determination

Step II: Preparation gel base.

Step III: Preparation & Evaluation Nanoemulgel:

Evaluation of Nanoemulgel:

- Physical Examination
- Drug content determination
- pH determination
- Spreadability
- Viscosity measurements and rheological behavior
- In -vivo studies
- In -vitro drug release kinetics
- Skin irritation studies
- Microbiological assay
- Stability studies
- Comparison with marketed formulation

6. Importance of study/ Society application:

International status:

- **US Patent: US 6004566 A** Topical and transdermal delivery system utilizing submicron oil spheres.
- **US Patent**; **US 5547677 A** oil in water antimicrobial nanoemulsions for oropharyngeal application as a spray or mouthwash.
- **WO 2003000243 A1** an antimicrobial oil in water nanoemulsion which could be either used as a toothpaste or as a mouthwash for the treatment of oral mucositis.

National Status:

- Lakshmana P S, Sharvanan S, Aravindan S, Bhuvaneswari A, Manikandan V. Nanoemulgel for Transdermal Delivery of Cyclobenzaprine Hydrochloride: Design, Characterization and *In-Vitro* Studies. Novel Approaches in Drug Designing Development. 2017; 1(5) : 555575

Significance of the study:

Nanoemulgel possesses gel characteristic with improved nanoemulsion properties for topical application. Other advantages of nanoemulgel include its low skin irritation, increase permeability and high drug-loading capacity for topical delivery when compared with the other carriers such as microemulsions, liposomes or solid lipid nanoparticles. This colloidal delivery system can be utilized to incorporate drug compounds to target on bioavailability improvement, increase stability plateau and reducing their side effects. The outcome of different studies on permeability, pharmacokinetic, pharmacodynamic and safety profile of the drugs delivered topically through nanoemulgel.

7. Proposed work Plan/ Formulation and Structure of Study:

Year-wise Plan of work and targets to be achieved:

Sr. No.	**Expected target to be achieved**	**1-6 months**	**7-9 months**	**10-12 months**	**13-16 months**	**17--30 months**	**31- 33 months**	**34-36 Months**
01	Literature survey	Literature survey						
02	Selection and collection of drug and excipients	Selection and collection of drug and excipients						
03	Preformulation Studies	Preformulation Studies						
04	Design, development and optimization	Design, development and optimization						
05	Evaluation of Nanoemulgel	Evaluation of Nanoemulgel						
06	Statistical Analysis, Data Interpretation and Conclusions	Statistical Analysis, Data Interpretation and Conclusions						
07	Publishing Research and submitting data	Publishing Research and submitting data						

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